## REMARKS

Claims 1-4, 10, 16, 19 and 21 are pending in this application. Claims 1 and 4 are canceled. Claim 16 is amended to recite a "detecting" step. Claim 21 is amended to recite that the claimed alteration "comprises a null mutation in a CCN1 allele." Upon entry of these amendments, claims 10, 16, 19 and 21 are pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Support for amended claim 16 can be found throughout the specification, with exemplary support at paragraph [0071]. Support for amended claim 21 may be found, e.g., at paragraph [0061] of the specification. Accordingly, Applicant respectfully submits that no new matter has been added.

### I. Patentability Arguments

A. The Enablement Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

The Examiner has withdrawn the previous rejection of claim 19 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. However, at page 2 of the Office Action new grounds of rejection for claim 19 are set forth by the Examiner. Specifically, the Examiner alleges that "the specification does not disclose, and the art does not teach any correlation between mutations in the *CCN1* gene and the development of AVSDs in any animal, nor do they teach that elimination of one or both *CCN1* alleles is a naturally occurring mutation leading to AVSD." Further, the Examiner alleges that "[j]ust because such a mutation results in a phenotype in an experimental animal model does not in itself render the animal model useful for identifying agents that could modulate the development of AVSD..." Therefore, the Examiner alleges that the specification does not enable the full scope of claim 19.

Applicant respectfully disagrees with the Examiner. An *in vivo* animal model correlates with a specific condition if one of ordinary skill in the art would accept the model as reasonably correlating to the condition. *See* MPEP 2164.02. If the art is such that a particular model is

recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate - even with such evidence, the Examiner must weigh the evidence for and against correlation. *See* MPEP 2164.02. Moreover, "a rigorous correlation is not necessary where the [disclosed] activity is reasonable based upon the probative evidence." *See Cross v Iizuka*, 735 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir 1985).

As taught by the instant specification, the relevant prior art indicated that AVSD can be inherited as a single gene defect located within a 12 cM region located on chromosome 1 (1p21-p31). *See* specification, paragraph [0013]. The instant specification discloses that the *CCN1* gene is located within this region and has been mapped to chromosome 1 (1p22-p31). *See* specification, paragraph [0015]. Moreover, *CCN1*$^{+/-}$ transgenic mice "display a phenotype similar to human AVSD with incomplete penetrance and variable expressivity." *See* specification, paragraph [0029]. Thus, *CCN1*$^{+/-}$ mice constitute "a rare mouse model displaying heterozygous cardiac phenotype with single gene mutation, in accordance with the autosomal dominant inheritance observed in most human CHDs." *See* specification, paragraph [0030]. The Examiner cites Maslen, Curr. Opin. Cardiol., 19:205-210 (2004)(hereinafter "Maslen") to support the alleged lack of correlation. However, Applicant respectfully submits that Maslen actually supports the viability of *CCN1*$^{+/-}$ transgenic mice as a model for AVSD in all animals. At page 207, 2$^{nd}$ column, 3$^{rd}$ paragraph, Maslen points out that "[s]ome of the most powerful means of identifying genes involved in heart development have been through genetically manipulated animal models…[a]s a result, there has been a recent explosion of information regarding the biochemical pathways that regulate atrioventricular septation." While Maslen does warn that genetic knockout and gene ablasion studies may not be directly analogous to the genetic etiology of heart defects in humans, that statement is founded on the observation that "the models are usually created by introducing severe genetic abnormalities such as complete elimination of gene expression, often resulting in embryonic lethality." *See* Maslen, page 208, 2$^{nd}$ column, 1$^{st}$ paragraph. *CCN1*$^{+/-}$ transgenic mice, as noted *supra*, do not display embryonic lethality; rather, *CCN1*$^{+/-}$ mice display an AVSD phenotype mirroring that in humans and consequently avoid the purported pitfalls mentioned in Maslen.

The Examiner also alleges that the disclosed AVSD phenotype "may not be a result of the disruption of the [CCN1] gene itself." The Examiner cites a portion of Scarff *et al.*, Genesis,

36:149-157 (2003) to support this proposition (hereinafter "Scarff"). The Examiner has improperly focused on a single sentence culled from an obscure reference to the exclusion of overwhelming evidence provided by the specification and pertinent prior art. In fact, the portion of Scarff cited by the Examiner is directed to retention of the selectable marker gene in knock-out mice and consequently is not relevant to the instant disclosure which describes mice in which the reporter gene has been "knocked-into" the Cyr61 genomic sequence. As stated by Scarff, "much less is known about the impact of the retention of a neomycin selectable marker cassette on the expression of "knock-in" reporter genes." Scarff is one of only three studies showing that selection of a neomycin cassette can alter the expression of a reporter gene. In each study, GFP was the reporter gene – there is no prior art disclosure that retention of a neomycin cassette is capable of affecting expression of β-galactosidase. Moreover, each study discloses only that retention of a neomycin cassette may alter the expression level of a reporter gene. According to Scarff, tissue specific expression patterns were not altered in mice bearing the neomycin cassette and the Examiner has failed to cite any prior art disclosing an altered phenotype arising from retention of a neomycin cassette. On the contrary, one of ordinary skill in the art understands that knock-in mice, as disclosed by the instant specification, are an art-accepted model system for analyzing gene function during development as well as in disease (e.g. AVSD). The aforementioned, in view of: (i) Maslen's disclosure that a single gene defect located in the same region of chromosome 1 as Cyr61 results in the disclosed phenotype (Maslen, page 206, 1st column, 2nd paragraph); (ii) Maslen's disclosure that a putative cell adhesion protein is a susceptibility gene for AVSD (Maslen, page 206, 2nd column, 1st paragraph); and (iii) Maslen's disclosure that AVSD is classified as a disease of the extracellular matrix (ECM) (Maslen, page 207, 2nd column, last paragraph bridging page 208), Applicant respectfully submits that the evidence of record, considered as a whole, overwhelmingly leads to the conclusion that the observed phenotype results from disruption of Cyr61. In view of the foregoing, Applicant respectfully submits that the rejection of claim 19 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn and hereby requests the Examiner withdraw the rejection

The Examiner has withdrawn the previous rejection of claim 21 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. However, at page 5 of the Office Action new grounds of rejection for claim 21 are set forth by the Examiner.

Specifically, the Examiner now alleges that "[j]ust because the complete absence of CCN1 function leads to abnormal development of the vascular system in an artificially created animal model, does not mean that alterations in the CCN1 gene are the cause of AVSDs." Further, the Examiner alleges that Maslen "clearly teaches a multifactorial origin with multiple genes simultaneously involved, with…none shown to be causal or associated with sporadic AVSD."

Applicant respectfully disagrees with the Examiner and submits that the Examiner has mischaracterized Maslen. In relevant part, Maslen states that "several families have been reported to have autosomal-dominant AVSD with incomplete penetrance, demonstrating that AVSD can be inherited as single gene defect" (emphasis added). *See* Masler, page 206, column 1, 2nd paragraph. Moreover, Masler points out that "there are two established genetic loci for isolated AVSD," one of which maps to chromosome 1 (1p31-p21). *See Ibid.* As noted *supra*, *CCN1* is within this locus. The instant disclosure provides a transgenic mouse model establishing that reduced expression (i.e., haploinsufficiency) of a single gene, *CCN1*, is sufficient to result in AVSD.

The Examiner further alleges that the instant specification provides "no reference or guidance to what type of alteration one of skill in the art should look for." Applicant respectfully disagrees with the Examiner; however, to expedite prosecution, claim 21 is amended to specify a null mutation, i.e., a loss of function mutation. The present application demonstrates through a working example that a null mutation results in a predisposition to the claimed phenotype. One of ordinary skill in the art understands that all null mutations are functionally equivalent and would therefore predict that all null mutations would produce equivalent phenotypes. To the extent the Examiner's reasoning related to the unpredictability of mutations in *CCN1* generally, the rejection is now moot. In view of the foregoing, Applicant respectfully submits that the rejection of claim 21 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn and hereby requests the Examiner withdraw the rejection.

B. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner, at page 7 of the Office Action has rejected claims 1, 4, 10 and 16 under 35 U.S.C. § 102(b) as allegedly anticipated by Mo *et al.*, Mol. Cell Biol., 22:8709-8720 (2002) (hereinafter "Mo *et al.*"). The Examiner characterizes Mo *et al.* (on page 6 of the Office Action) as "teach[ing] a method of producing, identification, and isolation of transgenic mice (and

embryos) whose genome (sic) comprise heterozygous or homozygous disruptions of the CCN1 gene and testing the transgenic mice for their genotype."

Applicant cancels claims 1 and 4. Accordingly, the rejections under 35 U.S.C. § 102(b) directed thereto are rendered moot. With respect to the remaining rejections, Applicant respectfully traverses.

Applicant amends claim 16 to recite a detecting step. Applicant respectfully points out to the Examiner that: (1) Mo *et al.* contains no description of any cardiovascular defects, nor is any attempt made to characterize transgenic mice comprising heterozygous disruptions of *CCN1*; (2) Mo *et al.* teaches that "*Cyr61* heterozygotes were viable and fertile"; and (3) the instant specification teaches that *Cyr61* heterozygotes do "not exhibit any apparent phenotype." (emphasis added). Consequently, as the specification points out, the detection of AVSD in $CCN1^{+/-}$ mice was "surprising." *See* specification, paragraph [0070]. In light of the foregoing, Applicant respectfully submits that one of ordinary skill in the art, at the time the application was filed, would have no motivation for testing $CCN1^{+/-}$ mice for the presence of an AVSD. Therefore, the Examiner lacks a basis in fact and/or technical reasoning to support a determination that detection and identification of $CCN1^{+/-}$ mice having an AVSD "necessarily flow from the teachings of the prior art" as required when the Examiner, as here, is "relying upon the theory of inherency." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990.

Moreover, even if, as Examiner suggests, Mo *et al.* can be said to "teach analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry" Applicant respectfully submits that such disclosure would not "necessarily have resulted in the determination of AVSD." The specification teaches that 35% of $CCN1^{+/-}$ mouse embryos do not exhibit an AVSD phenotype. *See* specification, paragraph [0071]. Because analyzing β-galactosidase expression in any of the 35% of $CCN1^{+/-}$ mouse embryos that do not exhibit an AVSD phenotype would not have resulted in the determination of AVSD, such a determination cannot "necessarily flow from the teachings of the prior art." The Examiner is reminded that "inherency may not be established by probabilities or possibilities." *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

Because Mo *et al.* fails to disclose: (1) a step for "testing" a $CCN1^{+/-}$ mouse for the presence of an AVSD, (2) a step for "detecting" an AVSD in a $CCN1^{+/-}$ mouse, and (3) a step for "identifying" a $CCN1^{+/-}$ mouse that has an AVSD, Mo *et al.* fails to meet the standard for an

inherent disclosure and cannot anticipate claims 1, 4, 10 or 16 under 35 U.S.C. § 102(b). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 1, 4, 10 and 16 under 35 U.S.C. § 102(b).

F. 35 U.S.C. § 103(a)

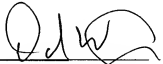
Applicant notes that the Examiner has withdrawn the rejections of claims 1-4 and 21 under 35 U.S.C. § 103(a).

**II. Conclusion**

In view of the foregoing amendments and remarks, Applicant respectfully submits that the claims are now in condition for allowance and early notification thereof is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY, LLP

By: 

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